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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,061	09/24/2004	Hiroharu Arakawa	HIR-117	1525
7590 04/16/2008 H. Jay Spiegel & Associates, P.C. P.O. Box 11 Mount Vernon, VA 22121-0011			EXAMINER MCINTOSH III, TRAVIS C	
			ART UNIT 1623	PAPER NUMBER
			MAIL DATE 04/16/2008	DELIVERY MODE PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/509,061

**Applicant(s)**

ARAKAWA ET AL.

**Examiner**

TRAVISS C. MCINTOSH III

**Art Unit**

1623

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 02 January 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1, 11, 12, 14 and 34 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1, 11, 12, 14 and 34 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/S508)  
Paper No(s)/Mail Date 1/2/08
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

The Amendment filed 1/2/2008 has been received, entered into the record, and carefully considered. The following information provided in the amendment affects the instant application by:

Claims 1, 11, 14, and 34 have been amended.

Claims 2-10, 13, and 15-33 have been canceled.

Remarks drawn to rejections of Office Action mailed 10/15/2007 include:

Claim objections: which have been overcome by applicant's amendments and have been withdrawn.

Double Patenting Rejection: which has been maintained for reasons of record.

102 (b) rejection: which has been overcome by applicant's amendments and has been withdrawn.

103(a) rejection: which has been maintained for reasons of record.

An action on the merits of claims 1, 11-12, 14, and 34 is contained herein below. The text of those sections of Title 35, US Code which are not included in this action can be found in a prior Office action.

### ***Double Patenting***

The rejection of claims 1, 11-12, 14, and 34 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of Kojiri et al. (U.S. Patent No. 5,922,860) in view of Fukuda et al. (Synergism between Cisplatin and Topoisomerase I

inhibitors, NB-506 and SN-38 in Human Small Cell Lung Cancer Cells”, Cancer Research, 56, 789-93, 2/15/1996) is maintained for reasons of record.

The claims of the instant application are drawn to combinations of an indolocarbazole of formula Ia and an additional anticancer agent, such as cisplatin.

Kojiri et al. teach that compounds having the same formula as those of formula Ia of the instant application and their use as antitumor agents. What is not taught is the combinations with additional anticancer agents.

Fukuda et al. disclose synergistic combinations of NB-506 and cisplatin (see abstract – discussion on page 791). NB-506 is a structurally similar compound to that of compound of formula Ia instantly claimed. Fukuda et al. state that the combination of cisplatin and a topoisomerase I inhibitor is a very interesting strategy for cancer chemotherapy (discussion).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the topoisomerase I inhibitors of Kojiri et al. in combination with cisplatin with these references before them. Fukuda et al. discuss the potential for synergism in cancer therapy when using cisplatin and a topoisomerase I inhibitor. Moreover, it is noted that the compounds of formula Ia are very structurally similar to NB-506 as in Fukuda et al. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186

(*CCPA 1960*) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the art disclosed indolocarbazole of Kojiri et al. with another antitumor agent, especially in light of the synergistic effects shown by Fukuda et al. One would have been motivated to combine these agents to form a new composition which would be used for the very same purpose, as an antitumor agent. Moreover, it is noted that the KSR decision forecloses the decision that teaching/suggestion/motivation is required in making an obviousness rejection.

Applicants argue that Kojiri et al. do not teach any combinations. Applicants also argue that Fukuda teaches combinations of NB-506 and additional anticancer agents, but NB-506 is divergent in structure as compared to the instant compound of formula Ia. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner believes that due to the close structural relationship between NB-506 as set forth in Fukuda and formula Ia as in Kojiri, a skilled artisan would find it obvious to make a combination of anticancer drugs with the compound of Kojiri and additional agents of Fukuda with these references before them. Regarding applicant's arguments drawn to Fukuda only guessing about the synergistic effects, this would at the

minimum afford a skilled artisan an obvious reason to try to combine the agents as instantly claimed.

Applicants also argue that the structures of formula Ia and NB-506 are very different. The examiner respectfully disagrees. Regarding applicants noting that the instant compounds have -OH in the 2 and 10 positions and NB-506 has -OH in the 1 and 11 positions, it is noted that claim 1 of Kojiri states that the -OH groups can be either in the 1 and 11 positions or the 2 and 10 positions, thus providing obviousness and motivation to have -OH at either sets of locations. The other difference is groups attached to the exocyclic amino moiety, NH-CHO versus NH-CH(CH<sub>2</sub>OH)<sub>2</sub>. However, Kojiri et al. also bridges the gap as the results of Table 1 show compounds with NH-CHO group have slightly lower activity versus compounds with NH-CH(CH<sub>2</sub>OH)<sub>2</sub> groups attached. Thus rendering obvious and providing motivation to change the NH-CHO to a NH-CH(CH<sub>2</sub>OH)<sub>2</sub> group.

Regarding applicant's arguments drawn to a "synergistic combination", it is noted these limitations are not in the claims and as such are not deemed to render unobvious the instant rejection.

#### ***Claim Rejections - 35 USC § 103***

The rejection of claims 1, 11-12, 14, and 34 under 35 U.S.C. 103(a) as being unpatentable over Fukuda et al. (art of record) in view of Kojiri et al. US 5,922,860 is maintained for reasons of record.

The claims of the instant application are drawn to combinations of an indolocarbazole of formula Ia and an additional anticancer agent, such as cisplatin, and methods of treating cancer with the same.

Fukuda et al. disclose synergistic combinations of NB-506 and cisplatin (see abstract – discussion on page 791). Fukuda et al. state that the combination of cisplatin and a topoisomerase I inhibitor is a very interesting strategy for cancer chemotherapy (discussion). What is not taught is the specific compound of formula Ia.

Kojiri et al. teach that compounds having the same formula as those of formula Ia of the instant application and their use as antitumor agents (see claim 2, abstract, examples).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the topoisomerase I inhibitors of Kojiri et al. in combination with cisplatin with these references before them. Fukuda et al. discuss the potential for synergism in cancer therapy when using cisplatin and a topoisomerase I inhibitor. Moreover, it is noted that the compounds of formula Ia are very structurally similar to NB-506, as discussed above. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious.). See also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art

disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious). Thus it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the art disclosed indolocarbazole of Kojiri et al. with another antitumor agent, especially in light of the synergistic effects shown by Fukuda et al. One would have been motivated to combine these agents to form a new composition which would be used for the very same purpose, as an antitumor agent. Moreover, it is noted that the KSR decision forecloses the decision that teaching/suggestion/motivation is required in making an obviousness rejection.

Applicants argue that Kojiri et al. do not teach any combinations. Applicants also argue that Fukuda teaches combinations of NB-506 and additional anticancer agents, but NB-506 is divergent in structure as compared to the instant compound of formula Ia. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner believes that due to the close structural relationship between NB-506 as set forth in Fukuda and formula Ia as in Kojiri, a skilled artisan would find it obvious to make a combination of anticancer drugs with the compound of Kojiri and additional agents of Fukuda with these references before them. Regarding applicant's arguments drawn to Fukuda only guessing about the synergistic effects, this would at the minimum afford a skilled artisan an obvious reason to try to combine the agents as instantly claimed.



Applicants also argue that the structures of formula Ia and NB-506 are very different. The examiner respectfully disagrees. Regarding applicants noting that the instant compounds have -OH in the 2 and 10 positions and NB-506 has -OH in the 1 and 11 positions, it is noted that claim 1 of Kojiri states that the -OH groups can be either in the 1 and 11 positions or the 2 and 10 positions, thus providing obviousness and motivation to have -OH at either sets of locations. The other difference is groups attached to the exocyclic amino moiety, NH-CHO versus NH-CH(CH<sub>2</sub>OH)<sub>2</sub>. However, Kojiri et al. also bridges the gap as the results of Table 1 show compounds with NH-CHO group have slightly lower activity versus compounds with NH-CH(CH<sub>2</sub>OH)<sub>2</sub> groups attached. Thus rendering obvious and providing motivation to change the NH-CHO to a NH-CH(CH<sub>2</sub>OH)<sub>2</sub> group.

Regarding applicant's arguments drawn to a "synergistic combination", it is noted these limitations are not in the claims and as such are not deemed to render unobvious the instant rejection. And these synergistic effects are not deemed unobvious as Fukuda et al. discusses synergism between their NB-506 compound and additional anticancer agents such as cisplatin.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TRAVISS C. MCINTOSH III whose telephone number is (571)272-0657. The examiner can normally be reached on M-F 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Traviss C McIntosh III/  
Examiner, Art Unit 1623  
April 14, 2008

/Shaojia Anna Jiang, Ph.D./

Supervisory Patent Examiner, Art Unit 1623